Ledipasvir/Sofosbuvir (Harvoni®) and Sofosbuvir/Velpatasvir (Epclusa®)

Criteria for Use

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.** *The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.*

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive sofosbuvir-based regimen without local adjudication.*

☐ Limited Life Expectancy

☐ Patients with severe renal impairment (eGFR<30mL/min/1.73m^2), end-stage renal disease or on hemodialysis (Refer to elbasvir/grazoprevir or Viekira CFU for this population if appropriate).

☐ Documented ongoing nonadherence to prescribed medications or medical treatment, failure to complete hepatitis C virus (HCV) disease evaluation appointments and procedures or unable to commit to scheduled follow-up/monitoring for the duration of treatment

☐ Known hypersensitivity to any component of the planned treatment regimen

Drug interactions

☐ For ledipasvir/sofosbuvir, coadministration with rifampin, rifabutin, rifapentine, St. John's wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, elvitegravir/cobicistat/emtricitabine/tenofovir, tipranavir/ritonavir, simeprevir, rosuvastatin, or amiodarone (refer to Issues for Consideration).

☐ For sofosbuvir/velpatasvir, coadministration with proton-pump inhibitors (unless medically necessary), rifampin, rifabutin, rifapentine, St. John's wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, tipranavir/ritonavir, rosuvastatin (greater than 10mg/day), topotecan, efavirenz, or amiodarone (refer to Issues for Consideration).

When a sofosbuvir-containing regimen is used in combination with ribavirin

☐ Any contraindications and/or intolerance to ribavirin if sofosbuvir-containing regimen to be used in combination with ribavirin

- Contraindication and/or intolerance to ribavirin: Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test, and men whose female partner is pregnant or plan to become pregnant, known hypersensitivity reaction, and/or significant anemia (i.e. symptomatic or baseline hemoglobin <10g/dL) and/or history of *significant* adverse events with previous ribavirin-containing regimen. **Please note that history of anemia related to ribavirin-containing regimen should be evaluated in context of PBM CFU for ESA (i.e., ribavirin dose reduction to 600mg must have been instituted prior to consideration of ESA use) and does not necessarily constitute intolerance.

Inclusion Criteria *The answers to ALL OF THE FOLLOWING must be fulfilled in order to meet criteria.*

☐ Under care of and/or in collaboration with an experienced VA HCV practitioner

☐ Adherence counseling performed including laboratory follow-up and documented understanding by patient

☐ For ledipasvir/sofosbuvir, HCV Genotype 1, 4, 5, or 6

☐ For sofosbuvir/velpatasvir, HCV Genotype 2, 3 or mixed Genotype that includes 2 or 3 (refer to Issues for Consideration for use in GT1)

☐ Treatment regimen and duration based upon HCV Genotype and patient characteristics according to the dosage and administration section below

For women of childbearing potential receiving ribavirin or who have a male partner receiving ribavirin:

☐ When ribavirin (which is pregnancy category X) is used, the ribavirin should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Two effective methods of contraception should be used during treatment with ribavirin, and for 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time

Dosage, Administration

Treatment regimen and duration are based upon patient characteristics as described in the Table below**.**

Ledipasvir/sofosbuvir regimen (i.e., two-drug fixed-dose combination product)

One tablet (90mg of ledipasvir and 400mg of sofosbuvir) taken orally once daily with or without food

Sofosbuvir/velpatasvir regimen (i.e., two-drug fixed-dose combination product)

One tablet (400mg of sofosbuvir and 100mg velpatasvir) taken orally once daily with or without food

When sofosbuvir-containing regimen is used in combination with ribavirin therapy, ribavirin should be administered in 2 divided doses with food [<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day unless patient has decompensated cirrhosis (CTP B or C) in which case ribavirin 600 mg/day is recommended].

Population includes patients with HCV monoinfection, HCV/HIV-1 co-infection, or hepatocellular carcinoma (HCC)[a]	Dosage Regimens	Total treatment duration
HCV Genotype 1		
Treatment-naïve without cirrhosis[a]		
HCV RNA <6 million IU/mL	Ledipasvir/sofosbuvir	8 weeks
HCV RNA ≥6 million IU/mL	Ledipasvir/sofosbuvir	12 weeks
Treatment-naïve with cirrhosis	Ledipasvir/sofosbuvir	12 weeks
Treatment-experienced[b] without cirrhosis	Ledipasvir/sofosbuvir	12 weeks
Treatment-experienced[b] with cirrhosis[c]	Ledipasvir/sofosbuvir and ribavirin OR Ledipasvir/sofosbuvir (if ribavirin contraindication/intolerant)	12 weeks 24 weeks
Decompensated cirrhosis	Ledipasvir/sofosbuvir and ribavirin (initiate ribavirin at 600mg/day and titrate up as tolerated) OR Ledipasvir/sofosbuvir (if ribavirin contraindication/intolerant)	12 weeks 24 weeks
HCV Genotype 2		
Without cirrhosis or with compensated cirrhosis (CTP A)[c]	Sofosbuvir/velpatasvir	12 weeks
Decompensated cirrhosis (CTP B or C)	Sofosbuvir/velpatasvir plus ribavirin[d]	12 weeks
HCV Genotype 3		
Without cirrhosis or with compensated cirrhosis (CTP A)[c]	Sofosbuvir/velpatasvir	12 weeks
Decompensated cirrhosis (CTP B or C)	Sofosbuvir/velpatasvir plus ribavirin[d]	12 weeks
HCV Genotype 4, 5, or 6		
Without cirrhosis or with compensated cirrhosis (CTP A)	Ledipasvir/sofosbuvir	12 weeks
Decompensated cirrhosis (CTP B or C)	Ledipasvir/sofosbuvir plus ribavirin (initiate ribavirin at 600mg/day and titrate up as tolerated)	12 weeks

[a]HCV/HIV co-infected patients who are treatment-naïve without cirrhosis should receive 12 weeks of ledipasvir/sofosbuvir independent of baseline HCV RNA; consideration should be given to using 12 week treatment courses in African Americans and those with 4-week on treatment HCV RNA >LLOQ.

[b]In clinical trials, treatment-experienced was defined as previous peginterferon/ribavirin with or without an NS3/4A protease inhibitor

[c]Refer to Issues for Consideration for additional information regarding treatment in cirrhosis

[d]FDA labeling recommends weight-based ribavirin dosage regimen; however, consider initiating ribavirin at 600mg/day and titrate up as

tolerated based upon expert opinion.

Recommended Monitoring

In addition to standard clinical and laboratory monitoring in a patient receiving HCV therapy, the following monitoring is recommended for sofosbuvir-based regimens:

- **Hematologic adverse events (anemia) if co-administered with ribavirin:** Complete blood count should be obtained at baseline and at treatment weeks 2, 4, 8, and 12, and at other time points, as clinically appropriate. Initial management of anemia should consist of ribavirin dose reduction for hemoglobin <10g/dL or sooner if clinically indicated; for additional monitoring and management of Hepatitis C treatment-related anemia refer to the PBM CFU for Recombinant Erythropoietin.
- Virologic monitoring **should be assessed to determine response to treatment. Patients receiving any sofosbuvir-based regimen should have HCV RNA assessed at week 4 of treatment; if the HCV RNA is quantifiable (>LLOQ) at week 4 or at any time point thereafter, HCV RNA should be reassessed in 2 weeks. If the repeated HCV RNA level has increased (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all therapy should be strongly considered.**
- **Sustained Viral Response (SVR) or non-response** should be determined by measurement of HCV RNA 12 weeks after stopping treatment.
- **Ongoing assessment of treatment adherence** including medical appointments, laboratory follow-up and medications should be performed.
- **Monthly pregnancy tests** for women of childbearing potential receiving ribavirin

Issues for Consideration

Treatment Considerations:

- **In genotype 1,** only use sofosbuvir/velpatasvir if LDV/SOF, GZR/ELB or OPrD regimen cannot be used (e.g., resistance, ribavirin required but intolerant). In genotype 1 patients who are treatment experienced with compensated cirrhosis and intolerant to ribavirin, SOF/VEL for 12 weeks may be used as an alternative.
- **In genotype 1 patients who had previous virological failure with an NS3-4A protease inhibitor,** ledipasvir/sofosbuvir has been shown to be effective. A 12 week regimen is FDA-approved for non-cirrhotic subjects who have failed prior HCV treatment (including regimens with a protease inhibitor) and 24 weeks of ledipasvir/sofosbuvir is FDA-approved regimen for cirrhotic subjects who have failed prior treatment. However, in a randomized, double-blind study comparing ledipasvir/sofosbuvir plus ribavirin for 12 weeks to ledipasvir/sofosbuvir for 24 weeks in cirrhotic patients who had previously failed NS3-4A protease-inhibitor based triple therapy with boceprevir or telaprevir; SVR was achieved in 96% (74/77) of patients treated with ledipasvir/sofosbuvir plus ribavirin for 12 weeks and in 75/77 (97%) of patients treated with ledipasvir/sofosbuvir for 24 weeks.
- **In genotype 1 patients who had previous virological failure with a sofosbuvir-based regimen,** in a Phase II trial of GT1-infected patients (29% of whom had cirrhosis) who initially failed SOF + PEG-IFN + RBV (n=25) or SOF + RBV (n=21), re-treatment with LDV/SOF + RBV for 12 weeks achieved SVR in 100% (25/25) with prior SOF + PEG-IFN + RBV experience and 95% (20/21) with prior SOF + RBV experience. The optimal treatment for patients who have failed an NS5A inhibitor-containing regimen is not known. Consultation with an expert is recommended.
- **In genotype 2 patients**,
    - In ASTRAL-2 a phase III, open-label, randomized, controlled trial among patients infected with genotype 2, patients were randomized to 12 weeks of either SOF/VEL (n = 134) or SOF + RBV (n = 132). 14% had cirrhosis and 15% had previous treatment experience. Overall SVR was 99% (133/134) with SOF/VEL compared with 96% (124/132) with SOF + RBV; SVR in treatment-naïve patients with cirrhosis, was 100% (15/15) with SOF/VEL compared with SVR 93% (14/15) in the SOF + RBV arm; SVR in treatment-experienced patients without cirrhosis was 100% (15/15) with SOF/VEL compared to 81% (13/16) with SOF + RBV. Consultation with an expert is recommended for treating decompensated patients who cannot tolerate ribavirin.
- **In genotype 3 patients**
    - In ASTRAL-3 a prospective, randomized, phase III trial of treatment naïve and experienced, SOF/VEL for 12 weeks (n = 277) was compared to SOF + RBV for 24 weeks (n = 275) among treatment-naïve and -experienced (PEG-IFN + RBV) patients infected with HCV GT3. SVR in cirrhotic patients receiving SOF/VEL was 91% compared to 97% in those without cirrhosis. SVR among treatment-experienced patients receiving SOF/VEL was 90% compared with 97% among those who were treatment-naïve. In patients with cirrhosis who were treatment-naïve and treatment-experienced, SVR rates were 93% (40/43) and 89% (33/37), respectively. Of patients with baseline resistance testing performed, 16% (43/274) had detectable NS5A RAPs and 88% (38/43) achieved SVR; SVR was 97% (225/231) in patients without baseline NS5A RAPs. SVR was 84% (21/25) in patients with the Y93H polymorphism at baseline; FDA labeling reports relapse rates of 33% (3/9) in GT3 patients with compensated cirrhosis and 6% (4/71) in patients without baseline NS5A RAPs.
    - Baseline testing for NS5A RAPs is suggested for GT3 treatment-experienced (including PEG/riba only) and/or cirrhotic patients to determine the need for ribavirin. If the Y93H RAP is present, then the addition of ribavirin should be strongly considered (expert opinion).
    - Consultation with an expert is recommended for treating decompensated patients who cannot tolerate ribavirin.

Use in Specific Populations (refer to Prescribing Information for comprehensive list of use in specific populations):

- **HIV:** Co-infected patients should be managed in consultation with an experienced HIV provider.
- **Decompensated cirrhosis: Treatment of patients with decompensated cirrhosis should be managed by physicians with extensive experience in the treatment of patients with advanced liver disease**
- **Hepatocellular Carcinoma (HCC) or other cancer:** It is reasonable to treat HCV in any patient with HCC, history HCC, or other malignancy *if there is a high likelihood that the cancer has been controlled. In most cases, this can be interpreted as no evidence of recurrence for 12 months or longer.*

- **Hepatic Impairment:** Ledipasvir/sofosbuvir or sofosbuvir/velpatasvir: No dosage adjustment is necessary for patients with mild, moderate or severe hepatic impairment.
- **Pre-liver transplant (also see decompensated cirrhosis and HCC bullet above): <u>The decision to treat *any* patient awaiting transplantation should be made in consultation with the transplant center where the patient is listed and determined on a case by case basis</u>**. Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation (pre- or post-) or whether treatment is appropriate given patient's prognosis.
- **Post-liver transplant: Any sofosbuvir-based regimen should only be used in patients who are being actively managed by physicians with extensive experience in the treatment of post-transplant patients**. Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation.
- **Renal Impairment:** Ledipasvir/sofosbuvir or sofosbuvir/velpatasvir: No dosage adjustment is necessary for patients receiving ledipasvir/sofosbuvir with mild or moderate renal impairment (i.e., eGFR>30 mL/min/1.73m^2); The major metabolite of sofosbuvir is renally excreted and will accumulate in subjects with eGFR <30 mL/min/1.73m^2.The safety and efficacy of fixed-dose combinations have not been adequately studied in patients with severe renal impairment (eGFR<30mL/min/1.73m^2), end-stage renal disease or on hemodialysis.
- **Substance or Alcohol Use**: All patients should be evaluated for current alcohol and other substance use, with validated screening instruments. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists as needed. **Thus, automatic disqualification of patients as treatment candidates based on a specific length of abstinence is unwarranted and is strongly discouraged**.
- **Mental Health Conditions:** HCV-infected patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder), as documented by psychiatric evaluation, who are engaged in mental health treatment should be considered for therapy on a case-by-case basis. Patients should be managed in collaboration with Mental Health providers to determine the risks versus benefits of treatment and potential treatment options.
- **Hepatitis B:** No safety and efficacy data are available in this population; prescribing information states that no dosage adjustments are needed for ledipasvir/sofosbuvir or sofosbuvir/velpatasvir for patients receiving tenofovir, entecavir or lamivudine. For patients receiving tenofovir disoproxil fumarate, monitor for tenofovir-associated adverse reactions.

Drug-interactions:

- Consult the prescribing information prior to use of sofosbuvir-based regimen for potential drug interactions
    - Sofosbuvir, ledipasvir, and velpatasvir are substrates of drug transporter P-gp and breast cancer resistance protein (BCRP); drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir, ledipasvir and velpatasvir plasma concentrations.
    - Ledipasvir and velpatasvir are inhibitors of the drug transporter P-gp and BCRP while velpatasvir is also an inhibitor of OATP1B1, OATP1B3, and OATP2B1; co-administration with substrates of these transporters may increase concentrations.
- Drugs that increase gastric pH are expected to decrease absorption and blood concentration of ledipasvir and velpatasvir
    - Separate antacids and ledipasvir/sofosbuvir or sofosbuvir/velpatasvir administration by 4 hours.
    - H2-receptor antagonists may be administered simultaneously with or 12 hours apart from ledipasvir/sofosbuvir or sofosbuvir/velpatasvir at a dose that does not exceed doses comparable to famotidine 40mg twice daily. If possible, consideration should be given to discontinuing the H2-receptor antagonists.
    - Proton-pump inhibitor doses comparable to omeprazole 20mg or lower can be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions. However, co-administration of omeprazole or other proton-pump inhibitors are not recommended with sofosbuvir/velpatasvir. If possible, consideration should be given to discontinuing the PPI during SOF/VEL treatment. If the PPI is deemed medically necessary, sofosbuvir/velpatasvir should be administered with food and taken 4 hours before omeprazole 20mg/day OR consider using daclatasvir+sofosbuvir±ribavirin as an alternative regimen.
- **Bradycardia with amiodarone coadministration:** Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with LDV/SOF or SOF/VEL is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended. Refer to prescribing information for additional details.

Education and Screening:

- Counsel patient on general liver health, especially abstaining from alcohol use and limiting acetaminophen use to 2g/day.
- Assess if patient previously screened and/or vaccinated for Hepatitis A and Hepatitis B vaccines; consideration vaccination if appropriate.
- Assess if patient previously screened for HIV; if not, consider testing for HIV.

Additional Resources:

- Refer to VA Office of Public Health Intranet Site http://vaww.hepatitis.va.gov

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